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Letter

Multi-cancer early detection: a new paradigm for reducing cancer-specific and all-cause mortality

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Guideline-based cancer screening does not reduce all-cause mortality in part because persons presenting for screening face much higher risks of dying of other cancers. With new technologies that can simultaneously screen for multiple deadly cancers, reductions in both cancer-specific and all-cause mortality may be within long-term reach.

DeGregori et al. suggest that cancer-specific mortality is the gold-standard primary endpoint of a cancer screening trial and that failure to demonstrate a reduction in all-cause mortality should not diminish advances in cancer screening (DeGregori et al., 2020). This topic was raised with reference to the recently published results from the NELSON lung cancer screening trial (de Koning et al., 2020), in which a reduction in lung cancer mortality was accompanied by no significant difference in all-cause mortality. An observation that DeGregori et al. did not make is that the major reason for the equivalence in all-cause mortality between the screened and control arms of the study is the high rate of deaths due to other (e.g., non-lung) cancers. Cancer caused the majority (56%) of all deaths in the study, and non-lung cancers caused about 1.7 times more deaths than lung cancer (35% non-lung cancer versus 21% lung cancer) (de Koning et al., 2020). These results are not unexpected in a study limited to heavy smokers, who are well-understood to be at elevated risk of lung cancer and a variety of other cancers (Islami et al., 2018). These data suggest that in populations screened for lung cancer, hard-won reductions in lung cancer deaths can be overshadowed by deaths due to other cancers.

New genomic technologies to simultaneously screen for multiple cancer types are under development (Liu et al., 2020; Lennon et al., 2020; Srivastava and Hanash, 2020), giving rise to a new paradigm of multi-cancer early detection (MCED). These approaches complement existing evidence-based cancer screening guidelines that address cancer one anatomic region at a time. To quantify differences in risks of cancer types that are targeted and not targeted by contemporary screening guidelines, we obtained the most recent cancer incidence and mortality rates available from the United States Surveillance, Epidemiology, and End Results (SEER) Program (SEER Program, 2020). As the United States Preventive Services Task Force (USPSTF) currently recommends the following cancer screening in the general population—biennial mammography for women aged 50–74, cervical cancer screening for women aged 21–64, and colorectal cancer screening for persons aged 50–79—we quantified for each of these target populations the rates of incidence and death due to cancers other than the one being screened. We found that in each of these populations, incidence and death rates for cancers other than the one being screened are 2- to 24-fold higher (Table S1). For persons eligible for colorectal cancer screening, incidence and death rates of cancers other than colorectal cancer are 11-fold higher than those for colorectal cancer. Altogether, these data suggest that persons presenting for guideline-recommended screening face substantially higher risks of being diagnosed or killed by cancer types arising in anatomic regions not addressed by those guidelines.

Existing screening guidelines do not cover the cancer types responsible for three-quarters of all cancer deaths and two-thirds of all cancer diagnoses (SEER Program, 2020). A broad set of these cancer types have been shown to be detectable simultaneously by new, noninvasive blood tests analyzing circulating cell-free nucleic acids or other analytes (e.g., proteins), which are the centerpieces of the new MCED paradigm. A number of these tests are in development (Liu et al., 2020; Lennon et al., 2020; Chen et al., 2020) and detect, across stages, cancers including but not limited to appendiceal, anal, bladder, colorectal, esophageal, head and neck, kidney, liver, lung, ovarian, pancreatic, stomach, and thyroid, as well as lymphoma and myeloma, that altogether account for a majority of cancer deaths. Importantly, MCED tests offer this broad detection with a single, low false-positive rate of less than 1%. This is in contrast to existing single-cancer screens which, if implemented sequentially, can have a cumulative false-positive rate of 49%–60% (Croswell et al., 2009). A recent model of annual screening of the SEER population aged 50–79 with one particular MCED test (Liu et al., 2020) suggests that, among persons with cancers detected, the proportion of late-stage (III and IV) cancers could drop by 78%, corresponding to a 39% reduction in 5-year cancer deaths, and an absolute reduction of 104 deaths per 100,000 persons screened (Hubbell et al., 2020). This absolute reduction in deaths would represent about 26% of cancer deaths and 7% of all-cause deaths per year in this age group (SEER Program, 2020).

Thus, given the potential for earlier diagnosis of cancers with higher cumulative prevalence than any single cancer, MCED could lead to substantial reductions in overall cancer mortality—and, by extension, measurable reductions in all-cause mortality. As DeGregori et al. point out, we cannot slow advances in cancer screening efforts by demanding evidence of reduction in all-cause mortality, but with new MCED approaches allowing us to screen simultaneously for multiple deadly cancers, it may be within our long-term reach.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.ccell.2021.02.004.

DECLARATION OF INTERESTS

C.A.C., E.H., and J.J.O. are employed at and have ownership interest in GRAIL, Inc.

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